

A novel RYR1 sequence variant in central core disease: A case report

Novel RYR1 sequence variant

Askeri Türken
Department of Physical Therapy and Rehabilitation, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Abstract

Muscular dystrophies are inherited diseases that cause progressive muscular weakness. Dystrophies are diagnosed with a biopsy, which histologically shows fiber size, areas of muscle necrosis, amounts of fat and connective tissue, however, genetic screening is definitive for the diagnosis of disease. Congenital myopathies are neuromuscular disorders that affect skeletal muscles used for movement. Muscles are relaxed by repeated contractions. In this case, a patient with central core disease is presented with novel alteration in the ryanodine receptor 1 (RYR1) gene after a 24-year delayed diagnosis. The mutation seen in our case occurred in the central region and caused central core disease. In conclusion, in the diseases, differential diagnosis should be considered a transition to a correct diagnosis, as they can imitate each other in cases such as complaints, laboratory and imaging.

Keywords

Muscular Dystrophy, Myopathy, Myotonia, Muscular Weakness, Ryanodine Receptor 1 Gene

DOI: 10.4328/ACAM.20875 Received: 2021-09-28 Accepted: 2021-10-27 Published Online: 2021-11-02 Printed: 2022-03-15 Ann Clin Anal Med 2022;13(Suppl 1): S46-48

Corresponding Author: Askeri Türken, Gazi Yaşargil Training and Research Hospital, Division of Physical Therapy and Rehabilitation, Diyarbakır, Turkey.

E-mail: askeriturken@hotmail.com P: +90 532 776 12 40 / +90 412 258 00 60 F: +90 412 258 00 50

Corresponding Author ORCID ID: <https://orcid.org/0000-0003-0638-8918>

Introduction

Central core disease (CCD) is a non-progressive, infrequent, congenital myopathy that causes weakness in the proximal muscles, which are closest to the center of the body, such as the muscles of the legs, upper arms, shoulder and pelvis [1]. Symptoms are generally observed during infancy, but may appear at any age. It clinically presents with mild hypotonia during early childhood, delayed motor skills, muscle weakness and gracility, frequent spinal deformities, skeletal malformations such as scoliosis and hip dislocation [2]. The clinical features of patient were consistent with the diagnostic features of the CCD. CCD is also allelic to malignant hyperthermia (MH) susceptibility [3].

Case Report

A 42-year-old female patient was admitted to the hospital with complaints of fainting and general muscle weakness during a sports competition. Less exercise was recommended considering fibromyalgia. Until the age of 42, when she came to the clinic, she was diagnosed in different departments with fibromyalgia, depression, rheumatoid arthritis, ankylosing spondylitis, polymyositis, epilepsy and multiple sclerosis. At the start of drug therapy for each diagnosis, the drugs were stopped when the patient's complaints increased. At the time of examination, her blood tests, Electromyography (EMG), and muscular biopsy results were normal. Demyelinating plaques were seen on brain and cervical magnetic resonance imaging (MRI). In the cerebrospinal fluid analysis, the third oligoclonal band was positive. The patient was diagnosed with multiple sclerosis (MS). Despite MS treatment, the patient's complaints never stopped and even increased. At her next visit, her creatine kinase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) enzymes were high, therefore the patient stopped taking MS treatment. In May 2019, the patient applied to the physical therapy and rehabilitation outpatient clinic with a complaint of pain in her right arm. In clinic examination, the general condition was good, the posture was normal, the arms were symmetrical when walking. There was mild weakness and rubbing in her right arm, and pallor of the skeletal muscles. Speech, swallowing and hearing were normal. Muscle Strength Rating Scale according to Oxford Scale Proximal muscle values were 4+/5. Mild myotonia was observed in the fingers, similar to spasticity, but not matching the definition of spasticity. Range of motion and superficial deep senses were normal. Bilateral Achilles reflexes were decreased. There was no pathological reflex. She had a clinic that had symptoms of the current diagnoses, but did not fit a differential diagnosis. Myopathy was suspected, and the patient was sent for gene analysis. Molecular analysis of the RYR1 gene revealed a Gly2394Ser mutation in exon 44, and this mutation has not been previously described in the literature. After the patient's history, physical and neurological evaluation, a gene analysis was requested, considering that it was not compatible with the diagnosis of MS, although MRI supported it, and it was more compatible with myopathy. As a result, the definitive diagnosis was CCD. A combined program of posture rehabilitation, balance-coordination and strengthening exercises was applied before and after the FAC and BI measurements. Pre-treatment:

Functional Ambulation Classification (FAC): 4, Post-treatment FAC: 5, Pre-treatment Barthel activities of daily living index score (BI): 90; Post-treatment BI: 100.

In this study, the informed voluntary consent form was taken from the patient for this case report.

Discussion

CCD is a slowly or non-progressive weakness congenital myopathy disease, characterized by hypotonia and delay in motor development in childhood [1,4]. It is autosomal dominantly-recessively inherited and has a frequency of 5-6: 100,000. CCD starts with weakness in the proximal muscles, especially in the lower proximal extremities and symmetrically affects both sides of the body

Although CCD is associated with malignant hyperthermia, muscle biopsies may be normal in some patients [5]. In general, the N-terminal and central regions are responsible for malignant hyperthermia

The patient's muscle biopsy, serum creatine phosphokinase level and EMG were normal. Magnetic resonance index (MRI) and cerebrospinal fluid (CSF) culture results were in favor of multiple sclerosis. The longest diagnosis period was MS for 24 years, and she received many treatments but her complaints did not improve, while CCD disease is caused by mutations in the C-terminal region [6,7]. In our case, c.7180A> G, corresponding to the p.Gly2394Ser mutation in the central region of the 44th exon of RYR1 gene caused the CCD disease.

Conclusion

Although there is no definitive treatment for core myopathies, supportive treatment is recommended. Rehabilitation is still the best treatment. Pain due to myotonia has been reported to be common [3]. In the examinations of the patient, the intense myotonic state due to myopathy was defined as spasticity that can develop in MS without considering the differential diagnosis. After the final diagnosis, the patient was prescribed carbamazepine up to 400 mg/day and 30 sessions of active rehabilitation program, the patient was given weight-free atrophy and correction of myotonic complaints in the presence of a physiotherapist, 1 session for 1 hour per day, taking into account the patient's compliance, participation and fatigue.

The mutation seen in our case occurred in the central region and caused CCD disease. This mutation is novel (p.Gly2394Ser in the 44th exon of RYR1 gene) in the literature. Central region mutations can also cause CCD disease.

In conclusion, in the diseases, differential diagnosis should be considered as a transition to the correct diagnosis, as they can imitate each other in cases such as complaints, laboratory and imaging.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Magee KR, Shy GM. A new congenital non-progressive myopathy. *Brain*. 1956;79(4):610-21.
2. Shuaib A, Paasuke RT, Brownell KW. Central core disease. Clinical features in 13 patients. *Medicine (Baltimore)*. 1987;66:389-96.
3. Solbakken G, Løseth S, Froholdt A, Eikeland TD, Nærland T, Frich JC, et al. Pain in adult myotonic dystrophy type 1: relation to function and gender. *BMC*. 2021; (1): 1-11.
4. Dubowitz, Victor. *Muscle disorders in childhood*. 2nd ed. London: Bailliere Tindall Limited; 1995.
5. McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. *Hum Mutat*. 2000; 15(5):410-17.
6. Jungbluth H. Central core disease. *Orphanet J Rare Dis*. 2007; 2(1):1-9.
7. Amburgey K, Bailey A, Hwang JH, Tarnopolsky MA, Bonnemann CG, Medne L, et al. Genotype phenotype correlations in recessive RYR1-related myopathies. *Orphanet J Rare Dis*. 2013; 8 (1):1-12.

How to cite this article:

Askeri Türken. A novel RYR1 sequence variant in central core disease: A case report. *Ann Clin Anal Med* 2022;13(Suppl 1): S46-48